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MYOCARDIAL INFARCTION AND TRANSFUSION REQUIREMENTS IN TRANSFUSION DEPENDENT ANEMIC PATIENTS

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The influence of myocardial infarction (MI) on the transfusion requirements of transfusion dependent patients has not been previously studied. We studied thirty frequently transfused patients on long-term hemodialysis and a similar number of age and sex matched patients who were infrequently transfused to ascertain the influence of MI on transfusion requirements. Patients with evidence of previous MI on EKG in the transfused and control groups were similar (40% and 36% respectively), which indicated that the

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presence of a prior MI did not of itself determine which long term dialysis patients were more likely to be transfusion dependent. In frequently transfused patients with MI the principal influence of MI was that there was the difference in the hemoglobin level (transfusion trigger) at which these patients were transfused was observed in comparison to those without MI (8.3 ± 1.5 g/dl vs. 6.9 ± 1 g/dl, p 0.01). Patients with MI require a higher level of hemoglobin than patients without MI and these patients should be carefully monitored for the adequacy of their hemoglobin level when they are transfusion dependent. Further studies will be needed to elucidate the mechanism responsible for the higher required hemoglobin level in frequently transfused patients with MI.

ABSTRACT

The influence of myocardial infarction (MI) on the transfusion requirements of transfusion dependent patients has not been previously studied. We studied thirty frequently transfused patients on long-term hemodialysis and a similar number of age and sex matched patients who were infrequently transfused to ascertain the influence of MI on transfusion requirements. Patients with evidence of previous MI on EKG in the transfused and control groups were similar (40% and 36%, respectively) which indicated that the presence of a prior MI did not of itself determine which long term dialysis patients were more likely to be transfusion dependent. In frequently transfused patients with MI the principal influence of MI was that there was the difference in the hemoglobin level (transfusion trigger) at which these patients were transfused was observed in comparison to those without MI (8.3 ± 1.5 g/dl vs. 6.9 ± 1 g/dl, $p<0.01$). Patients with MI require a higher level of hemoglobin than patients without MI and these patients should be carefully monitored for the adequacy of their hemoglobin level when they are transfusion dependent. Further studies will be needed to elucidate the mechanism responsible for the higher required hemoglobin level in frequently transfused patients with MI.

Key Words: Transfusion, hemodialysis, myocardial infarction, erythropoietin, transfusion trigger.

INTRODUCTION

Cardiac output is the major determinant of oxygen delivery when oxygen content is normal (1). If oxygen content falls because of a reduction in hemoglobin, an increase in cardiac output is the major compensatory mechanism (1). Myocardial infarction (MI) is the most common cause of chronic impairment in cardiac output (2,3) but there has been little investigation of the effects of MI on transfusion requirements. Patients on long term hemodialysis are chronically anemic due to depressed circulatory levels of erythropoietin (4), and they often require chronic transfusion support although the level of transfusion support varies widely in this population (5). Patients on long term hemodialysis also have a high incidence of myocardial infarction (6). Thus, patients on long term hemodialysis provide a suitable population inn which to study the influence of myocardial infarction on transfusion requirements.

We have previously reported (5) that there is a group of intensely transfused dialysis patients (ITD) that are essentially transfusion dependent. In the present study we undertook to compare the ITD population with a control population of patients on dialysis who were not intensely transfused with respect to the presence of MI. We sought to determine in what ways a previous MI in this setting influences transfusion practice and hemoglobin requirements. This study was performed just before the transition to erythropoietin therapy occured. It allowed us to critically evaluate transfusion practice with respect to MI patients so that subsequent therapy with

erythropoietin could be appropriately individualized.

METHODS

I. Dialysis Population

Sixty patients receiving hemodialysis at the Artificial Kidney Center of Rhode Island (AKC) were studied. The first 30 patients selected had received 5 or more transfusions within the previous six months. These patients were designated intensely transfused dialysis patients (ITD). The remaining 30 patients received no transfusions during this time and were designated as dialysis controls (DC). The dialysis controls were individually matched to the ITD group by sex, age and the number of months on dialysis.

II. Sample Collection

Blood for analysis was obtained from the patients at the AKC prior to the administration of heparin, transfusion or hemodialysis treatment.

III. Hematologic Measurements

Complete blood counts (CBC) were performed on a Coulter Counter model S. Platelet counts were performed on a Clay-Adams Ultra-flo 100. Differentials were counted manually. Reticulocyte counts were done by a standard new methylene blue dye method. The absolute reticulocyte count was determined by multiplying the RBC count by the percent of reticulocytes. The absolute lymphocyte count was determined by multiplying the WBC count by the percent of lymphocytes counted on the differential.

IV. Biochemical Measurements

Erythropoietin levels were measured in a competitive radioimmunoassay (Smith Kline Laboratories). Red blood cell ATP, 2,3-DPG and inorganic phosphorus were assayed using neutralized perchloric acid extracts of heparinized whole blood. ATP (7) and 2,3-DPG (7) levels were measured fluorometrically. Inorganic phosphorus was measured on a COBAS Chemistry Instrument using the Roche Reagent for Inorganic Phosphorus.

V. **EKG Analysis**

Routine EKGs were obtained on all patients. EKGs were classified into 2 groups: Those with EKG evidence of MI and those without such evidence. EKG interpretation was performed by a cardiologist who was otherwise not involved in the study.

VI. **Statistical Analysis**

The mean and standard deviation (SD) was reported for each group. The means of the two groups were compared by using the non-paired t-test. A p value of <0.05 was considered significant.

RESULTS

There were no significant differences between the groups in the parameters of age, sex and months on long-term hemodialysis, (Table I) but the two groups, as expected, differed significantly ($p<.001$) in terms of the total lifetime number of blood transfusions each had received (88.2 ± 10.3 vs. 4.3 ± 4.7 units) and their degree of iron overload as reflected in ferritin levels (Table II).

Table II also shows a comparison of the hematologic parameters of the ITD and the infrequently transfused dialysis control population as well as a comparison of both groups with normal values. These data are further subdivided as to the presence of MI in these groups. There were significant overall differences in the red blood cell counts and other parameters of red cell mass for ITD versus DC with the mean hematocrit of ITD and DC being 22.2 ± 4.2 vs 25.9 ± 5 relative to normal ($p<0.001$).

In patients who are not frequently transfused, there was no significant difference between the hemoglobin levels of those with MI versus those without MI (8.3 ± 1.2 vs. 8.7 ± 1.8). In contrast, there was a significant difference in the pre-transfusion hemoglobin of frequently transfused dialysis patients with MI versus frequently transfused patients without MI (8.3 ± 1.6 vs. 6.9 ± 1.1, $p< 0.01$).

The range of 2,3-DPG levels in ITD was greater than 2,3-DPG levels of either normals or DC. The 16.1% increase of ITD over DC (Table III) was not a significant difference, but the 25.4% increase over normals was significant ($p<0.05$).

DISCUSSION

In the present study, intensely transfused dialysis patients (ITD) were not more likely than matched less intensely transfused dialysis control patients to have had an MI (12 of 30 vs. 11 of 30) as demonstrated by the resting electrocardiogram. In the absence of abnormalities of electrolytes or calcium, the resting EKG is usually a reliable means to diagnose myocardial infarction (6) in dialysis patients. It was not possible to determine by the methods used which patients with MI might have residual ischemia, and it would be worthwhile in future studies to consider treadmill evaluation of patients with MI requiring blood transfusions (6).

The principal effect of MI on transfusion requirements in the ITD was a significantly higher baseline hemoglobin level ($p<0.01$) at the time MI patients required transfusion. These findings suggest oxygen delivery is more impaired in ITD patients with MI than oxygen delivery in ITD patients without MI. The influence of transfusion on oxygen delivery has not been studied rigorously in relation to transfusion requirements. Neff et al. (8) studied a large group of patients being maintained on long-term hemodialysis when their clinical condition was stable. The cardiac index of these patients was significantly elevated. A subset of patients were studied before and after progressive blood transfusion to hematocrits above 40 and there was a clear correlation between cardiac index and hematocrit in these patients ($r = 0.76$, $p<0.01$). A normal level of cardiac index was

reached in most patients at a hematocrit of 30% which is below the transfusion levels of the patients we studied.

Our study does not address myocardial function in the ITD patients with MI, but it is likely that the presence of an MI could further compromise left ventricular function of dialysis patients (9), and thus explain the need for higher hemoglobin levels in these patients. Previous studies (2,3) have shown that a spectrum of chronic hemodynamic abnormalities present singly or in different combinations in the post-infarction patient. These disorders include localized abnormalities of ventricular contraction, mitral regurgitation and low ejection fraction (2). A high resting ventricular filling pressure, low cardiac index and an increased end-diastolic volume commonly are associated with these conditions. Moraski et al. (3) concluded that the left ventricular ejection fraction (LVEF) is the most sensitive measurement of left ventricular function and subsequently Lai et al (10) showed that in a randomly selected dialysis population, left ventricular ejection fraction was less than 50% in 7 of 37 subjects (19%). Studies of LVEF in relation to baseline hemoglobin levels in the ITD population would be of interest to further define the contribution of decreased left ventricular function to the increased hemoglobin requirements of these patients.

Despite the relatively higher hemoglobin levels due to transfusion, ITD patients with abnormal EKGs still appeared to have residual deficiency in oxygen delivery since 2,3-DPG levels were significantly increased in MI patients (Table II). 2,3-DPG levels in ITD were not elevated to as high a level as that reported in other anemias (11,12) probably because of inhibition of 2,3-DPG synthesis by

chronic acidosis (11). It has been shown that in anemic subjects who are exercised, an important role is played by the oxygen dissociation curve as mediated by red cell 2,3-diphosphoglycerate levels (12). The work of Oski et al. (12) suggests that in individuals with high 2,3-DPG, e.g. pyruvate kinase deficient patients in whom there is a significant right shift of their oxyhemoglobin dissociation curve, there is less of a cardiac index increase in response to workload in contrast to patients with low 2,3-DPG levels in whom there is more need for cardiac compensation. Control of 2,3-DPG synthesis in patients on long-term dialysis is greatly influenced by pH as well as complex and possibly opposing effects of respiratory alkalosis, metabolic acidosis and phosphate levels. The role of increased 2,3-DPG in improving oxygen delivery in ITD patients with MI will need more comprehensive study before any conclusions can be reached as to whether the increased 2,3-DPG levels noted in MI patients contribute to improved oxygen delivery in this setting.

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Figure 1

The pretransfusion hemoglobin levels of a group of intensely transfused patients receiving hemodialysis with or without evidence of a prior myocardial infarction (MI).

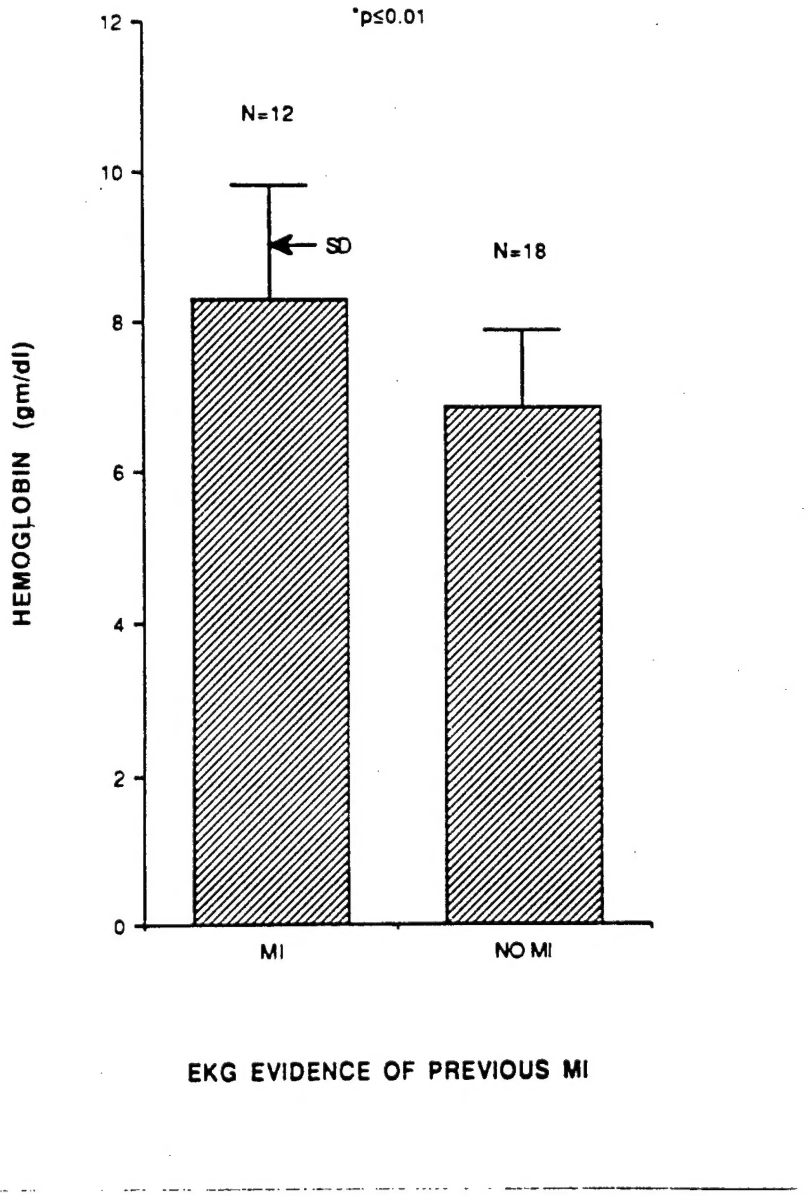

TABLE I

CHARACTERISTICS OF INTENSELY TRANSFUSED DIALYSIS PATIENTS (Group A) AND INFREQUENTLY TRANSFUSED CONTROL POPULATION (Group B)

PARAMETER	A. ITD			B. DIALYSIS		
	1. MI	2. No MI	All	1. MI	2. No MI	All
M/F	6/6	5/13	11/19	2/9	9/10	11/19
Number	12(40%)	18(60%)	30	11(36.7%)	19(63.3%)	30
Age	55.8 ± 148.2	52.2 ± 21.6	53.7 ± 20.3	62.1 ± 18.5	52.3 ± 17	55.9 ± 17.9
Months on Dialysis	36.8 ± 31.2	35.6 ± 33.2	36 ± 31.9	43.1 ± 36.2	39.1 ± 39.3	40.5 ± 37.6
Units Transfused	115.8^{+} ± 148.2	69.8^{o} ± 54.6	88.2^{x} ± 10	7 ± 5^{+*}	2.7 ± 3.9^{*o}	4.3 ± 4.7

$^{*+ox}$ $p < .01$
Mean ± SD

TABLE II

HEMATOLOGIC PARAMETERS OF THE ITD (Group A) AND DIALYSIS CONTROL (Group B) POPULATIONS

PARAMETER	A. ITD			B. CONTROLS			C. NORMALS
	1. MI^{x}	2. No MI^{o}	All	1. MI^{+}	2. No MI*	All	
N =	12	18	30	11	19	30	
Hematocrit, %	24.6 ± 4.6	20.6 ± 3.1	22.2 ± 4.2	24.7 ± 3.7	26.6 ± 5.6	25.9 ± 5.0	44.5 ± 3.8
Retics. x 10^{6}/ul	0.068 ± .03	0.052 ± .04	0.058 ± .03	0.081 ± 0.043	0.08 ± 0.05	0.083 ± 0.043	0.05 ± 0.012
Erythropoietin, mIU/ml	13.3 ± 5.7	11.6 ± 7.1	12.3 ± 6.5	24.5 ± 32.7	27.6 ± 28.9	26.4 ± 29.8	37 ± 11
Ferritin, ng/ml	1278 ± 4898	2004 ± 1876	2913 ± 3528	360.7 ± 641.4	129.5 ± 204.5	214.3 ± 425	136 ± 63

TABLE III

SPECIAL HEMATOLOGIC ASSAYS OF THE ITD (Group A) AND INFREQUENTLY TRANSFUSED (Group B) CONTROL DIALYSIS POPULATIONS

PARAMETER	A. ITD			B. CONTROLS			C. NORMAL*
	1. MI	2. No MI	ALL	1. MI	2. No MI	ALL	
N =	12	18	30	11	19	30	>100
2,3 DPG uM/gm Hb	20.2 ± 6.6	15.4 ± 3.5	17.3 ± 5.5	15.1 ± 6.6	14.7 ± 4.1	14.8 ± 5.1	13.8 ± 1.6
ATP, uM/gm HB	5.9 ± 1.2	5.8 ± 2.4	5.9 ± 2	6.2 ± 1.9	4.7 ± 1.6	5.3 ± 1.8	3.5 ± 0.5
Inorganic PO_4, mg/dl	4.9 ± 1.5	4.4 ± 2.3	4.6 ± 2	4.8 ± 1.3	4.7 ± 1.6	4.7 ± 1.5	3.5 ± 0.6

*A1 vs A2, $P < 0.05$

*Annual reference values, Naval Blood Research Laboratory